UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/630,070	07/30/2003	David R. Milich	VACCINE-07083	9382

7590 12/17/2004

Maha A. Hamdan
MEDLEN & CARROLL, LLP
Suite 350
101 Howard Street
San Francisco, CA 94105

EXAMINER	
MCGAW, MICHAEL M	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 12/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/630,070	MILICH ET AL.	
	Examiner	Art Unit	
	Michael M. McGaw	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *21-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☒ Claim(s) *17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is responsive to applicant's election filed October 26, 2004, electing to prosecute Group I, with the species election as indicated below. Thus, claims 1-13 and 16-20 are pending and under examination.

Election/Restrictions

Applicant's election of Group I, claims 1-20, in the reply filed on October 26, 2004 is acknowledged. Applicant did not indicate whether the election was made with or without traverse. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Additionally, Applicant was required to select a species for examination from the various species represented in claims 13-15. Applicant chose SEQ ID NO. 17 from claim 13 in response to the species election. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 21-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on October 26, 2004.

Specification

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is

requested in correcting any errors of which applicant may become aware in the specification.

Claim Objections

Claim 17 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. This claim is objected to for two reasons. First, claim 1 refers only to SEQ ID No. 38 while claim 17 would include other sequences as well. Second, claim 1 indicates that a heterologous antigen must be present while claim 17 removes this limitation.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 18, 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 ends with the phrase "said amino acid sequence comprising a loop region." The meaning of this phrase is not clear. It sounds as though Applicant is saying that the entire sequence forms a single loop. This cannot be true based upon what is known of core particles. While one might guess, based upon a little outside knowledge, that applicant is referring to the immunodominant loop region around resides 75-82, it

appears that the core particle forms loops at other positions along its sequence. (See for instance Fig. 1, pg. 64 of Pumpens, et al. (1995) or Fig. 1A, pg. 3107 of Jegerlenher et al.(2002), Fig. 1 of Pumpens et al. (2001), all cited by Applicant or see abstract of Koschel, M. et al. (1999),) Thus, "comprising a loop region" seems a very vague statement and it is not clear what Applicant is claiming. It is noted that Applicant refers to the "immunodominant B cell epitope" as being localized around amino acids and apparently forming a loop. It is not clear what the boundaries of the loop region are based on that statement and what others have said. For instance, Pumpens et al. (1999) refers to the immunodimnant loop as being from residues 78-82 (See pg. 3, col. 1, 3rd to last line). US 2003/0138769 A1 teaches the immunodominant loop at about residues 70-90 or more commonly referred to as being between 75 and 85 (paragraphs [0006] and [0151]).

Claim 2 indicates that the antigen is inserted in the loop region. Again, without knowing the identity of the loop, it is unclear where the insert is going.

Claim 18 states "A nucleic acid sequence encoding said heterologous antigen linked to the amino acid sequence set forth in SEQ ID NO:38 of Claim 1." The claim can be read as a nucleic acid sequence linked to an amino acid sequence. Is this what applicant intended? In the interest of compact prosecution the claim is being interpreted as a nucleic acid sequence encoding said heterologous antigen linked to SEQ ID NO:38.

Claim 19 states "An expression vector comprising the nucleic acid sequence of Claim 18." Due to the problems in claim 18 it is not clear what nucleic acid sequence

Applicant is referring to in claim 19. Does nucleic acid sequence of claim 18 mean only the "nucleic acid sequence encoding said heterologous antigen" or does Applicant mean a nucleic acid sequence encoding said heterologous antigen linked to SEQ ID NO:38? In the interest of compact prosecution the claim is being interpreted as specifying an expression vector comprising the nucleic acid sequence encoding said heterologous antigen linked to SEQ ID NO:38.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-12 and 16-20 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent Application Publication 2003/0138769 A1 to Birkett (cited by Applicant on form 1449).

Applicant claims a composition comprising a heterologous antigen linked to the amino acid sequence set forth in SEQ ID N0:38, said amino acid sequence comprising a loop region. SEQ ID NO: 38 is woodchuck hepatitis virus core particle sequence.

US 2003/0138769 A1 teaches immunogenic HBc chimer particles. At paragraph [0154] it is indicated that although the human ayw subtype is the preferred sequence,

the core sequence from woodchuck hepatitis virus can be used as well. The sequence is identified in that paragraph as SEQ ID No. 251. US Patent Application Publication No. 2003/0138769 A1 is a publication of Application No. 09/930,915. SEQ ID No. 251 of US Patent Application Publication No. 2003/0138769 A1 is 100% identical to SEQ ID No. 38 by sequence alignment (alignment not shown). Therefore claims 1, 12, 17 and 20 are anticipated. As to claims 2-7 the various insertion sites are known in the art and taught by US 2003/0138769 A1. See for instance paragraph [0067] discussing N-terminal, C-terminal and internal insertions as well as conjugated epitopes, paragraph [0151] for positions in and around the immunodominant loop, paragraph [0156] (and Koschel as referenced by US 2003/0138769 A1) for insertions at positions such as residue 44. The various positions are known in the art. See for instance Pumpens et al. (1995) at pg. 66, col. 1, 1st 4 sentences, Koschel et al., Pumpens, et al. (2001) pg. 106, col. 1, last full paragraph) As to claim 8, US 2003/0138769 A1 teaches the insertion of multiple epitopes (see for instance claim 19; see also Ulrich et al. pg. 153, last full paragraph). As to claim 9, Paragraph [0104] teaches heterolgous antigens linked via conjugation. As to claims 10 and 11, paragraph [0110] and claims 21-23 teach B cell and T cell epitopes. As to claim 13, US 2003/0138769 A1 teaches SEQ ID No. 38 with a C-terminal cysteine residue. (paragraph [0019]). Claims 14 and 15 are drawn to non-elected species. As to claim 16, the entire core molecule represents an immune enhancer sequence. For instance, US 2003/0138769 A1 teaches that the immune response was most vigorous when the antigen was inserted at the site of the immunodominant loop. Claim 18 has been rejected under 35 U.S.C. 112, 2nd and is not

capable of meaningful interpretation. Consequently, claim 19 is also not capable of interpretation.

As a final matter, it is asserted by the Examiner that it is widely recognized that woodchuck hepatitis B core antigen is recognized by those of ordinary skill in the art as largely analogous to and/or substitutable for human hepatitis B core antigen, as well as core antigen derived from other species. US 2003/0138769 A1 indicates as much at paragraph 154. Also see the following documents cited by applicant on Form 1449: Pumpens, P. et al. (1995) Intervirology ; Maruyama, T. et al. (1994) Gastroenterology; lew, Y. et al. (2001) J. Virol.; Chang, C. et al. (1994) J. Virol. Also see Galibert (1982) cited on Form 892.

Claim Rejections - 35 USC § 103

Claims 1-12 and 16-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pumpens, P. et al. (1995) (as cited by Applicant on Form 1449).

Pumpens teaches the utility of hepatitis B virus core antigen particles as epitope carriers. Pumpens teaches that human hepatitis B virus core antigen shows strong conservation with hepatitis core antigen sequences from other species. (see page 64, col. 2) In tables 1 through 3 of Pumpens a number of insertion sites are shown for heterologous antigens. These include, N-terminal, C-terminal and internal insertions. Pumpens also discusses some potential sites for insertions on page 66, col. 1. Pumpens makes two critical points on page 67. First, Pumpens reports “capsids formed by C-terminally truncated HBc monomers are less stable than the corresponding full-

length protein particles." Second, that "foreign insertions [at this site] are not only possible but also exert a stabilizing effect on chimeric HBCΔ derivatives..."

SEQ ID NO: 38 matches the published sequence for WHV as published by Galibert et al. (1982) J. Virol. 41:51-65. Therefore, it would be obvious to one of ordinary skill in the art that SEQ ID NO: 38 could be used as described above by Pumpens et al. (1995). One of ordinary skill in the art would have been motivated to use the sequence of WHV as found in SEQ ID NO: 38 because Pumpens, among many others, teach the strong similarity of WHV core antigen to the human counterpart. Pumpens also teaches the utility of the core molecule as an epitope carrier. One of ordinary skill in the art would have expected to achieve a hepatitis B virus core antigen sequence useful as an epitope carrier based upon the WHV sequence because the techniques involved were well-developed at the time of Applicant's invention. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pumpens et al. (1995) as applied to claims 1-12 and 16-20 above, and further in view of Zlotnick, A. et al. (1997).

Claim 13 is a Markush claim specifying the C-terminal sequence of the core particle. One of the elements in the grouping is a C-terminal cysteine residue.

Pumpens does not teach adding a C-terminal cysteine residue.

Zlotnick teaches adding a C-terminal cysteine residue to achieve the stabilizing

effect in a C-terminally truncated hepatitis B core antigen. Zlotnick's recombinant hepatitis B core (HBc) protein molecule self-assembled into particles (pg. 9558; 1st full paragraph). The particles were substantially free of binding to nucleic acids on expression in a host cell (pg. 9560; last full paragraph). Most importantly, the particles were more stable than particles formed from an otherwise identical HBC chimer that lacks the C-terminal cysteine residue(s) or in which a C-terminal cysteine residue present in the chimer molecule is replaced by another residue (pg. 9558; 1st and 2nd full paragraphs).

One of ordinary skill in the art would have been motivated to combine the teachings of Pumpens outlining this various uses of HBc as an epitope carrier with that of Zlotnick because it was well known that HBc chimeras with c-terminal deletions, while still capable of self-assembly, were less stable than their full-length counterparts and that by adding back amino acid residues to these c-terminal deletion one could achieve a more stable chimer, while Zlotnick teaches that the addition of a cysteine residue to an HBc c-terminal truncation results in enhanced stability. One of ordinary skill in the art would have expected achieve a more stable HBc chimera with a c-terminal truncation by the addition of a cysteine residue because Zlotnick teaches that the addition of a cysteine to the c-terminal of an HBc molecule with a c-terminal truncation results in enhanced stability. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Allowable Subject Matter

The prior art does not teach SEQ ID NO: 17, which was the elected species found in claim 13, appended to the C-terminal end of SEQ ID NO:38. The prior art does teach a sequence identical to SEQ NO:38 with a C-terminal cysteine residue as found in the Markush group listed in claim 13.

Response to Amendment

It is noted that Applicant has amended method claim 25 to include the limitations of composition claim 1 and cancelled claim 31.

Conclusion

Claims 1-13 and 16-20 are rejected. Claims 14 and 15 are drawn to non-elected species.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Ulrich, R. et al. Core particles of hepatitis B virus as carrier for foreign epitopes (1998) Advances in Virus Research, vol. 50:141-182.

Pumpens, P. et al. Hepatitis core particles as a universal display model : a structure-function basis for development (1999) FEBS Letters, vol. 442:1-6.

See also the included Form 892.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael M. McGaw whose telephone number is (571)

272-2902. The examiner can normally be reached on Monday through Friday from 8 A.M. to 5 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

M. M.

Friday, December 03, 2004

JAMES HOUSEL 12/13/04
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600